Generation of Functional Thymic Epithelium from Human Embryonic Stem Cells that Supports Host T Cell Development.

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Public Summary:
A key organ that helps instruct the immune system on the difference between self and non-self is the thymus. This process of self versus non-self discrimination is referred to as immunological tolerance and is a critical problem to overcome for stem cell based therapies. In this paper, we describe a novel method that involves differentiating human stem cells into thymic epithelial cells (TEC's). We also demonstrate that these TEC's can help form a thymus in a mouse model system that results in productive T cell development. Furthermore, we also show that developing T cells from this model system are functional. This new technique may have broad applications for improving stem cell transplants by helping preventing immune rejections of such cells.

Scientific Abstract:
Inducing immune tolerance to prevent rejection is a key step toward successful engraftment of stem-cell-derived tissue in a clinical setting. Using human pluripotent stem cells to generate thymic epithelial cells (TECs) capable of supporting T cell development represents a promising approach to reach this goal; however, progress toward generating functional TECs has been limited. Here, we describe a robust in vitro method to direct differentiation of human embryonic stem cells (hESCs) into thymic epithelial progenitors (TEPs) by precise regulation of TGFbeta, BMP4, RA, Wnt, Shh, and FGF signaling. The hESC-derived TEPs further mature into functional TECs that support T cell development upon transplantation into thymus-deficient mice. Importantly, the engrafted TEPs produce T cells capable of in vitro proliferation as well as in vivo immune responses. Thus, hESC-derived TEP grafts may have broad applications for enhancing engraftment in cell-based therapies as well as restoring age- and stress-related thymic decline.